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(21) International Application Number: PCT/US00/11823 (22) International Filing Date: 1 May 2000 (01.05.00) (30) Priority Data: 60/183,039 4 May 1999 (04.05.99) US 09/552,630 19 April 2000 (19.04.00) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/552,630 (CON) Filed on 19 April 2000 (19.04.00) (71) Applicants (for all designated States except US): AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07840 (US). LIGAND PHARMACEUTICALS, INC. [US/US]; 10275 Science Center Drive, San Diego, CA 92121 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): COLLINS, Mark, A. [GB/US]; 1011 New Hope Street, 13B, Norristown, PA 19401 (US). MACKNER, Valerie, A. [US/US]; 1300 Butler Pike, Apartment #262, Conshohocken, PA 19428 (US). ZHI, Lin [CN/US]; 7794 Roan Road, San Diego, CA 92129		(US). JONES, Todd, K. [US/US]; 546 Marview Drive, Solana Beach, CA 92075 (US). TEGLEY, Christopher, M. [US/US]; 478 Thunderhead Street, Thousand Oaks, CA 91360 (US). WROBEL, Jay, E. [US/US]; 15 Rosetree Lane, Lawrenceville, NJ 08648 (US). EDWARDS, James, P. [US/US]; 8723 Hesby Court, San Diego, CA 92129 (US). (74) Agents: KODROFF, Cathy, A. et al.; Howson and Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US). (81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(54) Title: 2,1-BENZISOTHIAZOLINE 2,2-DIOXIDES			
(57) Abstract			
<p>A progesterone receptor antagonist of formula (1) wherein R₁, and R₂ are each, independently, hydrogen, alkyl, substituted alkyl, hydroxy, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, heteroarylalkyl, and alkynyl; or R₁ and R₂ are taken together to form a ring and together contain -CH₂(CH₂)_nCH₂-, -CH₂CH₂CMe₂CH₂CH₂-, -O(CH₂)_pCH₂-, O(CH₂)_qO-, -CH₂CH₂OCH₂CH₂-, -CH₂CH₂NR₇CH₂CH₂-,; or R₁ and R₂ are a double bond, said double bond having two methyl groups bonded to the terminal end, having a cycloalkyl group bonded to the terminal end, having an oxygen bonded to the terminal end, or having a cycloether bonded to the terminal end; R⁵ is a trisubstituted phenyl ring having structure (z), or R⁵ is a five or six membered heteroaryl ring containing 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO₂ and NR⁶ or pharmaceutically acceptable salt thereof.</p>			

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2,1-BENZISOTHIAZOLINE 2,2-DIOXIDES

Background of the Invention

5 Intracellular receptors (IR) form a class of structurally related gene regulators known as "ligand dependent transcription factors" (R. M. Evans, *Science* **240**, 889, 1988). The steroid receptor family is a subset of the IR family, including progesterone receptor (PR), estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR).

10 The natural hormone, or ligand, for the PR is the steroid progesterone, but synthetic compounds, such as medroxyprogesterone acetate or levonorgestrel, have been made which also serve as ligands. Once a ligand is present in the fluid surrounding a cell, it passes through the membrane *via* passive diffusion, and binds to the IR to create a receptor/ligand complex. This complex binds to specific gene
15 promoters present in the cell's DNA. Once bound to the DNA the complex modulates the production of mRNA and protein encoded by that gene.

 A compound that binds to an IR and mimics the action of the natural hormone is termed an agonist, whilst a compound which inhibits the effect of the hormone is an antagonist.

20 PR agonists (natural and synthetic) are known to play an important role in the health of women. PR agonists are used in birth control formulations, typically in the presence of an ER agonist. ER agonists are used to treat the symptoms of menopause, but have been associated with a proliferative effect on the uterus which can lead to an increased risk of uterine cancers. Co-administration of a PR agonist reduces or ablates
25 that risk.

 PR antagonists may also be used in contraception. In this context they may be administered alone (Ulmann *et al*, *Ann. N.Y. Acad. Sci.* **261**, 248, 1995), in combination with a PR agonist (Kekkonen *et al*, *Fertility and Sterility* **60**, 610, 1993) or in combination with a partial ER antagonist such as tamoxifen (WO 95-9619997 A1
30 960704).

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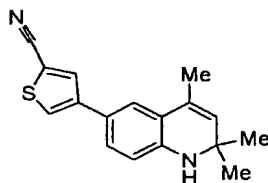
PR antagonists may also be useful for the treatment of hormone dependent breast cancers (Horwitz *et al*, Horm. Cancer, 283, pub: Birkhaeuser, Boston, Mass., ed. Vedeckis) as well as uterine and ovarian cancers. PR antagonists may also be useful for the treatment of non-malignant chronic conditions such as fibroids (Murphy *et al*, *J. Clin. Endo. Metab.* 76, 513, 1993) and endometriosis (Kettel *et al*, *Fertility and Sterility* 56, 402, 1991).

PR antagonists may also be useful in hormone replacement therapy for post menopausal patients in combination with a partial ER antagonist such as tamoxifen (US 5719136).

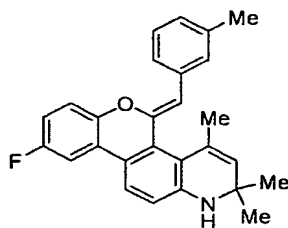
10 PR antagonists, such as mifepristone and onapristone, have been shown to be effective in a model of hormone dependent prostate cancer, which may indicate their utility in the treatment of this condition in men (Michna *et al*, *Ann. N.Y. Acad. Sci.* 761, 224, 1995).

Jones *et al* (US 5,688,810) is the PR antagonist dihydroquinoline A.

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**A**

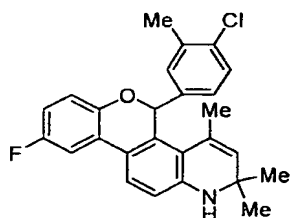
Jones *et al* described the enol ether **B** (US 5,693,646) as a PR ligand.

**B**

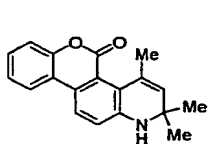
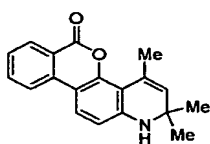
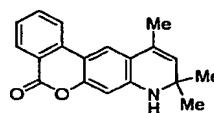
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Jones *et al* described compound **C** (US 5,696,127) as a PR ligand.

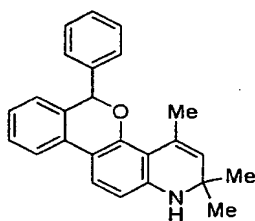
**C**

5 Zhi *et al* described lactones **D**, **E** and **F** as PR antagonists (*J. Med. Chem.* **41**, 291, 1998).

**D****E****F**

10

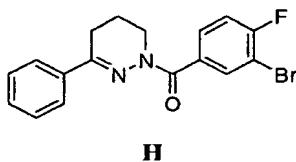
 Zhi *et al* described the ether **G** as a PR antagonist (*J. Med. Chem.* **41**, 291, 1998).

**G**

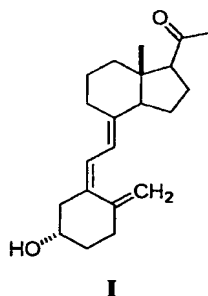
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 Combs *et al* disclosed the amide **H** as a ligand for the PR (*J. Med. Chem.* **38**, 4880, 1995).

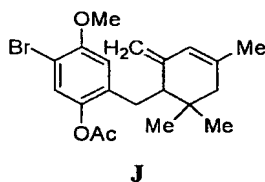
- 4 -



Perlman *et al* described the vitamin D analog **I** as a PR ligand (*Tetrahedron. Lett.* **35**, 2295, 1994).

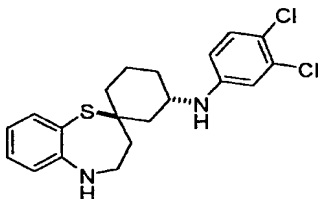


10 Hamann *et al* described the PR antagonist **J** (*Ann. N.Y. Acad. Sci.* **761**, 383, 1995).

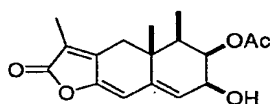


15 Chen *et al* described the PR antagonist **K** (Chen *et al*, POI-37, 16th Int. Cong. Het. Chem., Montana, 1997).

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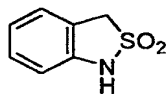
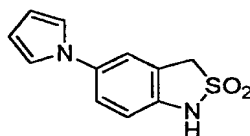
**K**

Kurihari *et al* described the PR ligand **L** (*J. Antibiotics* **50**, 360, 1997).

**L**

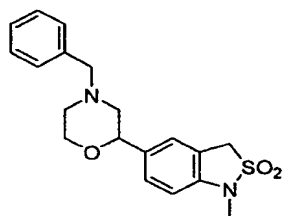
There are several examples of 2,1-benzisothiazoline 2,2-dioxides ('sultams') in the chemical and patent literature which contain no reference to progesterone activity, and do not carry the correct substitution pattern for PR modulator activity.

Chiarino *et al* described the preparation of the parent 2,1-benzisothiazoline 2,2-dioxide, i.e., **M** (and derivatives, e.g., **N**), that was used in the present invention (*J. Heterocycl. Chem.* **23**(6), 1645-9, 1986).

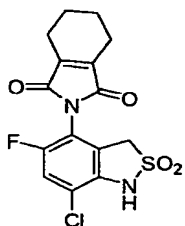
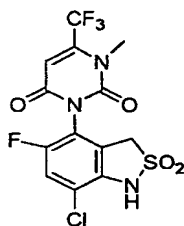
**M****N**

Skorcz *et al* described a series of 5-(2-morpholinyl)-2,1-benzisothiazolines, e.g., **O**, which are useful as central nervous depressants (U.S. 3,635,964).

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**O**

- 5 Kamireddy *et al* disclosed a series of cyclic sulfonamides, e.g., **P** and **Q**, useful for controlling undesired vegetation (WO 9533746).

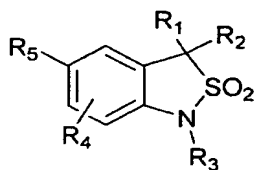
**P****Q**

10

Detailed Description of the Invention

This invention provides progesterone receptor antagonists of Formula 1 having the structure

15

**1**

- 7 -

wherein

R_1 , and R_2 are each, independently, hydrogen, alkyl, substituted alkyl, hydroxy, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, heteroarylalkyl, and alkynyl; or

- 5 R_1 and R_2 are taken together form a ring and together contain $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CMe}_2\text{CH}_2\text{CH}_2-$, $-\text{O}(\text{CH}_2)_p\text{CH}_2-$, $\text{O}(\text{CH}_2)_q\text{O}-$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{NR}_7\text{CH}_2\text{CH}_2-$; or

- R_1 and R_2 are a double bond, said double bond having two methyl groups bonded to the terminal end, having a cycloalkyl group bonded to the terminal end, having
10 an oxygen bonded to the terminal end, or having a cycloether bonded to the terminal end;

R_7 is hydrogen or alkyl of 1-6 carbon atoms;

$n = 1-5$;

$p = 1-4$;

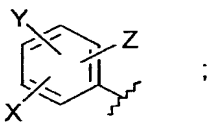
- 15 $q = 1-4$;

R^3 is hydrogen, hydroxyl, NH_2 , alkyl, substituted alkyl, alkenyl, alkynyl, substituted or, COR^A ;

R^A is hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

- 20 R^4 is hydrogen, halogen, $-\text{CN}$, $-\text{NH}_2$, alkyl, substituted alkyl, alkoxy, alkoxy, aminoalkyl, or substituted aminoalkyl;

R^5 is a trisubstituted phenyl ring having the structure,



25

X is halogen, OH , $-\text{CN}$, alkyl, substituted alkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, $\text{S}(\text{O})\text{alkyl}$, $\text{S}(\text{O})_2\text{alkyl}$, aminoalkyl, substituted aminoalkyl,

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-NO₂, perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, thioalkoxy, -COR^B, -OCOR^B, or -NR^CCOR^B;

R^B is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

5 R^C is hydrogen, alkyl, or substituted alkyl;

Y and Z are each, independently, hydrogen, halogen, -CN, -NO₂, alkoxy, alkyl, or thioalkyl; or

10 R⁵ is a five or six membered heteroaryl ring containing 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO₂ and NR⁶ with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, NO₂ alkyl, alkoxy, aminoalkyl, COR^D, and NR^ECOR^D;

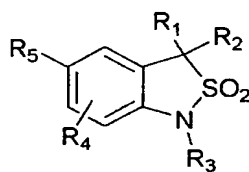
R^D is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

15 R^E is hydrogen, alkyl, or substituted alkyl;

R⁶ is hydrogen, alkyl, alkoxycarbonyl, or is absent when the nitrogen of NR⁶ is bonded to a ring double bond;

20 or pharmaceutically acceptable salt thereof, which are useful for contraception, in the treatment of fibroids, endometriosis, breast, uterine, ovarian and prostate cancer, and post menopausal hormone replacement therapy

Preferred compounds of this invention are those having the structure:



1

25 wherein

R₁ and R₂ are taken together form a ring and together contain -CH₂(CH₂)_nCH₂-;

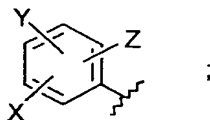
n = 2-3;

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R³ is hydrogen;

R⁴ is hydrogen;

R⁵ is a trisubstituted phenyl ring having the structure,



5

X is halogen, OH, -CN, alkyl, alkoxy, thioalkyl, substituted thioalkyl, S(O)alkyl, S(O)₂alkyl, aminoalkyl, substituted aminoalkyl, -NO₂, perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, or thioalkoxy;

10

Y and Z are each, independently, hydrogen, halogen, -CN, -NO₂, alkoxy, alkyl, or thioalkyl; or

R⁵ is a five or six membered heteroaryl ring containing 1, 2, or 3 heteroatoms selected from the group consisting of O, S, and NR⁶ with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, NO₂, alkyl, or alkoxy;

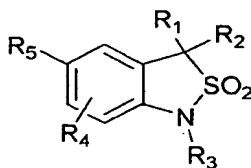
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R⁶ is hydrogen, alkyl, alkoxycarbonyl, or is absent when the nitrogen of NR⁶ is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof.

20

More preferred compounds of this invention are those having the structure



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wherein

R₁ and R₂ are taken together form a ring and together contain -CH₂(CH₂)_nCH₂- ;

25

- 10 -

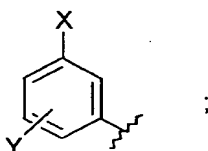
$n = 2-3$;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is a disubstituted phenyl ring having the structure,

5



X is halogen, -CN, or -NO₂ ;

Y is hydrogen, halogen, -CN, -NO₂, alkoxy, alkyl, or thioalkyl; or

- 10 R^5 is a five or six membered heteroaryl ring containing a heteroatom selected from the group consisting of O, S, and NR⁶ with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, or NO₂ ;

- 15 R^6 is hydrogen, or is absent when the nitrogen of NR⁶ is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof.

- 20 The compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereoisomers. While shown without respect to stereochemistry in Formula 1, the present invention includes such optical isomers and diastereoisomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

- 25 The term "alkyl" is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having 1-6 carbon atoms; "alkenyl" includes both straight- and branched-chain alkyl group of 2-6 carbon atoms containing at least one carbon-carbon double bond; "alkynyl" group includes both straight- and

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branched-chain alkyl group of 2-6 carbon atoms with at least one carbon-carbon triple bond.

The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl as containing one or more substituents from the group including halogen, CN, OH, NO₂, amino, aryl, heterocyclic, substituted aryl, substituted heterocyclic, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, arylthio. These substituents may be attached to any carbon of alkyl, alkenyl, or alkynyl group provided that the attachment constitutes a stable chemical moiety.

The term "aryl" is used herein to refer to an aromatic system of 6-14 carbon atoms, which may be a single ring or multiple aromatic rings fused or linked together as such that at least one part of the fused or linked rings forms the conjugated aromatic system. Preferred aryl groups include phenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, phenanthryl groups.

The term "substituted aryl" refers to aryl substituted by one or more substituents from the group including halogen, CN, OH, NO₂, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

The term "heterocyclic" is used herein to describe a stable 4-14 membered monocyclic or polycyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group including N, O, and S atoms. The N and S atoms may be oxidized, as an N-oxide, sulfoxide, or sulfone. The heterocyclic ring also includes any polycyclic ring in which any of above defined heterocyclic rings is fused to an aryl ring. The heterocyclic ring may be attached at any heteroatom or carbon atom provided the resultant structure is chemically stable. Such heterocyclic groups include, for example, tetrahydrofuran, piperidinyl, piperazinyl, 2-oxopiperidinyl, azepinyl, pyrrolidinyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, indolyl, quinolinyl, thienyl, furyl, benzofuranyl, benzothieryl, thiamorpholinyl, thiamorpholinyl sulfoxide, and isoquinolinyl.

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The term "substituted heterocyclic" is used herein to describe a heterocyclic having one or more substituents selected from the group which includes halogen, CN, OH, NO₂, amino, alkyl, substituted alkyl, cycloalkyl, alkenyl, substituted alkenyl, alkynyl, alkoxy, aryloxy, substituted alkoxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

The term "thioalkyl" is used herein to refer to the SR group, where R is alkyl or substituted alkyl.

The term "alkoxy" is used herein to refer to the OR group, where R is alkyl or substituted alkyl.

The term "aryloxy" is used herein to refer to the OR group, where R is aryl or substituted aryl.

The term "alkylcarbonyl" is used herein to refer to the RCO group, where R is alkyl or substituted alkyl.

The term "alkylcarboxy" is used herein to refer to the COOR group, where R is alkyl or substituted alkyl. This term is also referred to as alkoxycarbonyl.

The term "aminoalkyl" refers to both secondary and tertiary amines wherein the alkyl or substituted alkyl groups may be either same or different and the point of attachment is on the nitrogen atom.

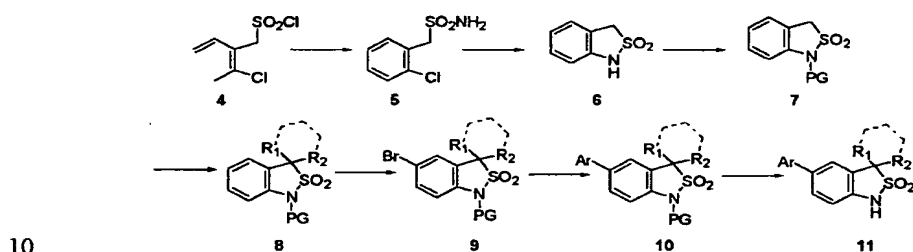
The term "halogen" is defined as Cl, Br, F, and I.

Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids. Salts may also be formed from inorganic bases, preferably alkali metal salts, for example, sodium, lithium, or potassium, and organic bases, such as ammonium, mono-, di-, and trimethylammonium, mono-, di- and triethylammonium, mono-, di- and tripropylammonium (iso and normal), ethyldimethylammonium, benzyldimethylammonium, cyclohexylammonium, benzylammonium, dibenzylammonium, piperidinium, morpholinium, pyrrolidinium, piperazinium, 1-methylpiperidinium, 4-ethylmorpholinium, 1-iso-

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propylpyrrolidinium, 1,4-dimethylpiperazinium, 1-n-butyl piperidinium, 2-methyl-piperidinium, 1-ethyl-2-methylpiperidinium, mono-, di- and triethanolammonium, ethyl diethanolammonium, n-butylmonoethanolammonium, tris(hydroxymethyl)methylammonium, phenylmonoethanolammonium, and the like.

- 5 The compounds of this invention were be prepared according to the following schemes from commercially available starting materials or starting materials which can be prepared using literature procedures. These schemes show the preparation of representative compounds of this invention.



Scheme 1

- 15 According to Scheme 1, commercially available sulfonyl chloride 4 is converted via the sulfonamide 5 to the 2,1-benzisothiazoline 2,2-dioxide 6 as described in the literature (Chiarino *et al*, *J. Heterocycl. Chem.* 23(6), 1645-9, 1986). The nitrogen atom of sultam 6 is then protected by a suitable protecting group, e.g., trimethyl silyl ethyl.

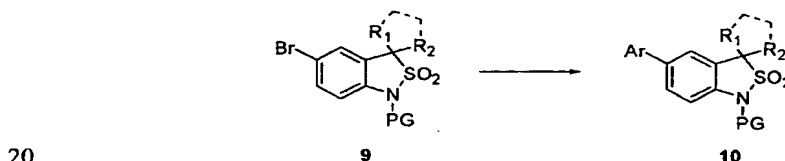
- 20 The protected sultam 7 next is treated with a strong organo-metallic base (e.g., butyl lithium, lithium diisopropylamide, potassium hexamethyldisilylazide) in an inert solvent (e.g., THF, diethyl ether) under nitrogen at reduced temperature (ca. -20 °C) (Kende *et al*, *Synth. Commun.* 12, 1, 1982). The resulting di-anion then is treated with excess electrophile such as an alkyl halide, preferably the iodide. If R₁ and R₂ are to be joined such as the product contains a spirocycle at position 3, then the electrophile
25 should be bifunctional, i.e., a diiodide. Subsequent bromination of the sultam 8

- 14 -

proceeds regioselectively at room temperature with bromine in acetic acid (an organic co-solvent such as dichloromethane may be added as required) in the presence of sodium acetate, to give the aryl bromide 9. Judicious choice of reaction conditions may facilitate simultaneous removal of the protecting group at this step.

5 The bromide 9 then is reacted with a palladium salt (e.g., tetrakis(triphenylphosphine)palladium(0)), in a suitable solvent (e.g., THF, dimethoxyethane, ethanol, toluene) under an inert atmosphere (argon, nitrogen). The mixture then is treated with an arylboronic acid or arylboronic acid ester and a base (sodium carbonate, triethylamine, potassium phosphate) in water or fluoride source
10 (cesium fluoride) under anhydrous conditions at elevated temperature to give the biphenyl sultam 10. Finally, the protecting group is removed under appropriate conditions and the final product 11 is isolated and purified by standard means.

 If R_1 and R_2 are different then the intermediate is prepared by reacting the dianion of 7 with one equivalent of the electrophile R_1-X (X = leaving group, e.g.,
15 iodide). The resultant mono-alkylated compound may be then isolated and re-subjected to the reaction conditions using R_2-X , or alternatively used *in situ* for the second alkylation with R_2-X . Alternatively, if the desired product is to contain $R_2 = H$, then the isolated mono-alkylated intermediate is taken through the subsequent steps.



Scheme 2

Other methodologies also are available for coupling the aryl group, Ar, to the sultam platform: for example, reaction of the bromide 9 with an aryl stannane, aryl zinc, or aryl magnesium halide in the presence of a palladium or nickel catalyst
25 (Scheme 2). The required aryl-metallic species are formed *via* standard techniques. Furthermore, the bromide 9 may be converted to an aryl boronic acid *via* standard procedures (treatment with *n*-butyllithium followed by addition of trimethyl borate and

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subsequent boronic ester hydrolysis) that will then undergo the range of previously described coupling procedures with a suitable aryl bromide.

The antiprogestational activity of the compounds of this invention was demonstrated in an in vitro standard pharmacological test procedure which evaluated the antiprogestational potency of a representative compound of this invention by measuring its effect on PRE-luciferase reporter activity in CV-1 cells co-transfected with human PR and PRE-luciferase plasmids. The procedure used and results obtained are described in Example 2 below.

The results obtained in this standard pharmacological test procedure demonstrate that the compounds of this invention are progestational antagonists, and are therefore useful as oral contraceptives (male and female), in hormone replacement therapy (particularly when combined with an estrogen), in the treatment of endometriosis, luteal phase defects, benign breast and prostatic diseases and prostatic, breast, ovarian, uterine and endometrial cancers.

The compounds of this invention can be used alone as a sole therapeutic agent or can be used in combination with other agents, such as other estrogens, progestins, or androgens.

The compounds of this invention can be formulated neat or with a pharmaceutical carrier for administration, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmacological practice. The pharmaceutical carrier may be solid or liquid.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

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Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, lethicins, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds of this invention can also be administered orally either in liquid or solid composition form.

The compounds of this invention may be administered rectally or vaginally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a

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matrix containing the active ingredient. Other occlusive devices are known in the literature.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Based on the results obtained in the standard pharmacological test procedures, projected daily dosages of active compound would be 0.02 µg/kg - 750 µg/kg. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached; precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated. Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packaged powders, vials, ampoules, pre filled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

The following provides the preparation of a representative compound of this invention.

Example 1

5-(3-chlorophenyl)spiro[2,1-benzisothiazole-3(1H),1'-cyclohexane] 2,2-dioxide

To 1,3-dihydro-2,1-benzisothiazoline 2,2-dioxide (Chiarino *et al.*, *J. Heterocycl. Chem.* **23**(6), 1645-9, 1986) (0.74 g, 4.4 mmol) in anhydrous dichloromethane (minimum amount) at room temperature was added sequentially N,N-diisopropylethylamine (0.76 mL, 4.4 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (0.77 mL, 4.4 mmol). After 30 min, the reaction was poured into water (50 mL), the layers were separated, and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The organic layers were combined, washed with brine (30 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 1,3-dihydro-1-(2'-trimethylsilylethyl)-2,1-benzisothiazoline 2,2-dioxide (1.3 g, 99%) as an off-white solid. ¹H NMR (CDCl₃, 300MHz) δ 0.02 (s, 9 H), 0.97 (dd, 2 H, J = 8.3, 8.2

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Hz), 3.73 (dd, 2 H, $J = 8.2, 8.3$ Hz), 4.40 (s, 2 H), 5.08 (s, 2 H), 7.05 (d, 1 H, $J = 7.4$ Hz), 7.07 (dd, 1 H), 7.26 (d, 1 H, $J = 7.4$ Hz), 7.35 ('t', 1 H, $J = 7.6, 7.6$ Hz). MS ((+) APCI m/z 317 $[M+NH_4]^+$).

To 1,3-dihydro-1-(2'-trimethylsilylethyl)-2,1-benzisothiazoline 2,2-dioxide (1.3 g, 4.3 mmol) in anhydrous tetrahydrofuran (13 mL) at room temperature was added 1,5-diiodopentane (1.29 mL, 8.6 mmol). The mixture was cooled to -78°C and lithium bis(trimethylsilyl)amide (1.0 M solution in tetrahydrofuran, 17.3 mL, 17 mmol) was added. After 15 min, the reaction mixture was poured into water (50 mL), the layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with brine (30 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% ethyl acetate/hexane) on silica gel gave 1,3-dihydro-3-spirocyclohexyl-1-(2'-trimethylsilylethyl)-2,1-benzisothiazoline 2,2-dioxide (0.8 g, 51%) as an off-white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 0.00 (s, 9 H), 0.95 (dd, 2 H, $J = 8.3, 8.2$ Hz), 1.18-2.36 (m, 10 H), 3.72 (dd, 2 H, $J = 8.2, 8.3$ Hz), 5.06 (s, 2 H), 7.03 ('t', 1 H, $J = 7.8$ Hz), 7.06 (dd, 1 H, $J = 1, 7.6$ Hz), 7.18 (dd, 1 H, $J = 1.1, 7.6$ Hz), 7.28 (dt, 1 H, $J = 1.3, 7.7$ Hz). MS (EI) m/z 367 $[M]^+$.

To a stirred solution of 1,3-dihydro-3-spirocyclohexyl-1-(2'-trimethylsilylethyl)-2,1-benzisothiazoline 2,2-dioxide (0.8 g, 2.2 mmol) in glacial acetic acid (5 mL) at room temperature was added dropwise a solution of bromine (0.11 mL, 2.2 mmol) in glacial acetic acid (2.2 mL). After stirring for 10 min, anhydrous sodium acetate (0.18 g, 2.2 mmol) was added and the solution was concentrated *in vacuo*. The residue was dissolved in ethyl ether (50 mL) and washed sequentially with water (50 mL), aqueous saturated sodium bicarbonate solution (50 mL), water (50 mL) and brine (30 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% ethyl acetate/hexane) on silica gel gave a complex mixture of products (0.56 g) with identical TLC characteristics as a white foam. The mixture was used without further purification.

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A solution of the mixture containing 5-bromo-1,3-dihydro-3-spirocyclohexyl-1-(2'-trimethylsilylethyl)-2,1-benzisothiazoline 2,2-dioxide (0.56 g, 1.25 mmol) and tetrakis(triphenylphosphine)palladium(0) (100 mg) in toluene (25 mL) was stirred under a flow of nitrogen for 25 min. To the solution was added sequentially solutions of 3-chlorophenylboronic acid (0.4 g, 2.5 mmol) in absolute ethanol (5 mL) and potassium carbonate (0.35 g, 2.5 mmol) in water (5 mL). The mixture was heated to 80 °C for 16 h and allowed to cool. The reaction mixture was poured into aqueous saturated sodium bicarbonate solution (50 mL) and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with water (50 mL) and brine (30 mL) and dried over magnesium sulfate. The solution was filtered, concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (2% ethyl acetate/toluene) and then by HPLC to give the title compound (65 mg) as a low melting yellow foam. HPLC conditions: Zorbax PRO, C18, 10u, 15A, 50 x 250 mm; mobile phase composition and gradient program, 70% water/ 30% AcCN; flow rate, 100 mL/min; injection volume, 120 mg/3 mL MeOH; detection wavelength, 280 nm, 500 PSI; temperature, amb. ¹H NMR (DMSO-*d*₆, 300 MHz), δ 1.47-2.19 (m, 10 H), 6.87 (d, 1 H, *J* = 8.2 Hz), 7.38 ('d', 1 H, *J* = 8.1 Hz), 7.46 ('t', 1 H, *J* = 7.9, 7.7 Hz), 7.56 (dd, 1 H, *J* = 1.7, 8.2 Hz), 7.62 ('d', 1 H, *J* = 7.7 Hz), 7.71, ('d', 1 H, *J* = 1.7 Hz), 7.75 (bs, 1H), 10.55 (bs, 1 H). MS (EI) *m/z* 347 [M]⁺. Anal. Calcd for C₁₈H₁₈ClNO₂S: C, 62.15; H, 5.22; N, 4.03. Found: C, 59.84; H, 5.30; N, 3.57.

Example 2 – Biological Activity

The antiprogestational activity of the compound of Example 1 was demonstrated in a conventional pharmacological test.

Reagents

Growth medium: DMEM (BioWhittaker) containing 10% (v/v) fetal bovine serum (heat inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

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Experimental medium: DMEM (BioWhittaker), phenol red-free, containing 10% (v/v) charcoal-stripped fetal bovine serum (heat-inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

5 Test Procedure

Stock CV-1 cells were maintained in growth medium. Co-transfection was done using 1.2×10^7 cells, 5 mg pLEM plasmid with hPR-B inserted at SphI and BamHI sites, 10 mg pGL3 plasmid with two PREs upstream of the luciferase sequence, and 50 mg sonicated calf thymus DNA as carrier DNA in 250 ml. 10 Electroporation was carried out at 260 V and 1,000 mF in a Biorad Gene Pulser II. After electroporation, cells were resuspended in growth medium and plated in 96-well plate at 40,000 cells/well in 200 ml. Following overnight incubation, the medium was changed to experimental medium. Cells were then treated with reference or test compounds in experimental medium. Compounds were tested for antiprogesterational 15 activity in the presence of 3 nM progesterone. Twenty-four hours after treatment, the medium were discarded, cells were washed three times with D-PBS (GIBCO, BRL). Fifty ml of cell lysis buffer (Promega, Madison, WI) was added to each well and the plates were shaken for 15 min in a Titer Plate Shaker (Lab Line Instrument, Inc.). Luciferase activity was measured using luciferase reagents from Promega.

20 When evaluated in the above-described test procedure, the compound of Example 1 had an IC_{50} of 900 nM. The IC_{50} is the concentration of test compound that gives half-maximal decrease in 3 nM progesterone induced PRE-luciferase activity.

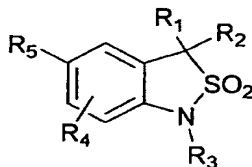
25 All publications cited in this specification are incorporated herein by reference herein. While the invention has been described with reference to a particularly preferred embodiment, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.

30

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WHAT IS CLAIMED IS:

1. A compound formula 1 having the structure



1

wherein

R₁, and R₂ are each, independently, hydrogen, alkyl, substituted alkyl, hydroxy, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, heteroarylalkyl, and alkynyl; or

R₁ and R₂ are taken together form a ring and together contain -CH₂(CH₂)_nCH₂-, -CH₂CH₂CMe₂CH₂CH₂-, -O(CH₂)_pCH₂-, O(CH₂)_qO-, -CH₂CH₂OCH₂CH₂-, -CH₂CH₂NR₇CH₂CH₂-, or

R₁ and R₂ are a double bond, said double bond having two methyl groups bonded to the terminal end, having a cycloalkyl group bonded to the terminal end, having an oxygen bonded to the terminal end, or having a cycloether bonded to the terminal end;

R₇ is hydrogen or alkyl of 1-6 carbon atoms;

n = 1-5;

p = 1-4;

q = 1-4;

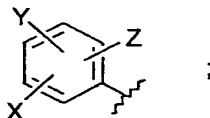
R³ is hydrogen, hydroxyl, NH₂, alkyl, substituted alkyl, alkenyl, alkynyl, substituted or, COR^A;

R^A is hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

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R^4 is hydrogen, halogen, -CN, -NH₂, alkyl, substituted alkyl, alkoxy, aminoalkyl, or substituted aminoalkyl;

R^5 is a trisubstituted phenyl ring having the structure,



X is halogen, OH, -CN, alkyl, substituted alkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, S(O)alkyl, S(O)₂alkyl, aminoalkyl, substituted aminoalkyl, -NO₂, perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, thioalkoxy, -COR^B, -OCOR^B, or -NR^CCOR^B;

R^B is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

R^C is hydrogen, alkyl, or substituted alkyl;

Y and Z are each, independently, hydrogen, halogen, -CN, -NO₂, alkoxy, alkyl, or thioalkyl; or

R^5 is a five or six membered heteroaryl ring containing 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO₂ and NR⁶ with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, NO₂, alkyl, alkoxy, aminoalkyl, COR^D, and NR^ECOR^D;

R^D is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

R^E is hydrogen, alkyl, or substituted alkyl;

R^6 is hydrogen, alkyl, alkoxycarbonyl, or is absent when the nitrogen of NR⁶ is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof.

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2. The compound according to claim 1, wherein
wherein

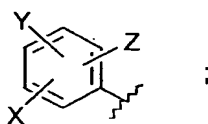
R_1 and R_2 are taken together form a ring and together contain $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$;

$n = 2-3$;

R^3 is hydrogen;

R^4 is hydrogen;

R^5 is a trisubstituted phenyl ring having the structure,



X is halogen, OH, -CN, alkyl, alkoxy, thioalkyl, substituted thioalkyl, S(O)alkyl, S(O)₂alkyl, aminoalkyl, substituted aminoalkyl, -NO₂, perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, or thioalkoxy;

Y and Z are each, independently, hydrogen, halogen, -CN, -NO₂, alkoxy, alkyl, or thioalkyl; or

R^5 is a five or six membered heteroaryl ring containing 1, 2, or 3 heteroatoms selected from the group consisting of O, S, and NR⁶ with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, NO₂, alkyl, or alkoxy;

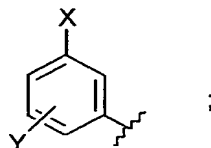
R^6 is hydrogen, alkyl, alkoxycarbonyl, or is absent when the nitrogen of NR⁶ is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof.

3. The compound according to claim 2, wherein

R^5 is a disubstituted phenyl ring having the structure,

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X is halogen, -CN, or -NO₂ ;

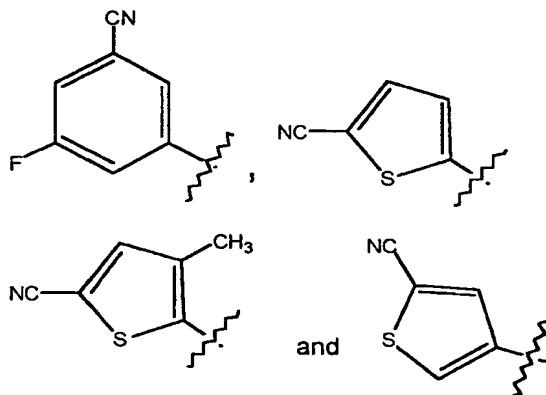
Y is hydrogen, halogen, -CN, -NO₂, alkoxy, alkyl, or thioalkyl; or

R⁵ is a five or six membered heteroaryl ring containing a heteroatom selected from the group consisting of O, S, and NR⁶ with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, or NO₂ ;

R⁶ is hydrogen, or is absent when the nitrogen of NR⁶ is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof.

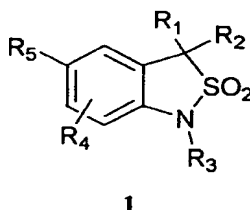
4. A compound of Claim 3 wherein R⁵ is selected from the group of:



5. The compound of claim 1, which is 5-(3-chlorophenyl)-spiro[2,1-benzisothiazole-3(1H),1'-cyclohexane] 2,2-dioxide or a pharmaceutically acceptable salt thereof.

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6. A method of providing progestational therapy to a mammal in need thereof which comprises administering a progestationally effective amount of compound formula 1 having the structure



wherein

R_1 , and R_2 are each, independently, hydrogen, alkyl, substituted alkyl, hydroxy, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, heteroarylalkyl, and alkynyl; or

R_1 and R_2 are taken together form a ring and together contain $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CMe}_2\text{CH}_2\text{CH}_2-$, $-\text{O}(\text{CH}_2)_p\text{CH}_2-$, $\text{O}(\text{CH}_2)_q\text{O}-$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{NR}_7\text{CH}_2\text{CH}_2-$; or

R_1 and R_2 are a double bond, said double bond having two methyl groups bonded to the terminal end, having a cycloalkyl group bonded to the terminal end, having an oxygen bonded to the terminal end, or having a cycloether bonded to the terminal end;

R_7 is hydrogen or alkyl of 1-6 carbon atoms;

$n = 1-5$;

$p = 1-4$;

$q = 1-4$;

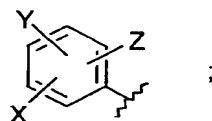
R^3 is hydrogen, hydroxyl, NH_2 , alkyl, substituted alkyl, alkenyl, alkynyl, substituted or, COR^A ;

R^A is hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

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R^4 is hydrogen, halogen, -CN, -NH₂, alkyl, substituted alkyl, alkoxy, aminoalkyl, or substituted aminoalkyl;

R^5 is a trisubstituted phenyl ring having the structure,



X is halogen, OH, -CN, alkyl, substituted alkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, S(O)alkyl, S(O)₂alkyl, aminoalkyl, substituted aminoalkyl, -NO₂, perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, thioalkoxy, -COR^B, -OCOR^B, or -NR^CCOR^B;

R^B is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

R^C is hydrogen, alkyl, or substituted alkyl;

Y and Z are each, independently, hydrogen, halogen, -CN, -NO₂, alkoxy, alkyl, or thioalkyl; or

R^5 is a five or six membered heteroaryl ring containing 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO₂ and NR⁶ with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, NO₂, alkyl, alkoxy, aminoalkyl, COR^D, and NR^ECOR^D;

R^D is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

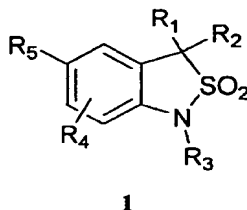
R^E is hydrogen, alkyl, or substituted alkyl;

R^6 is hydrogen, alkyl, alkoxycarbonyl, or is absent when the nitrogen of NR⁶ is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof to said mammal.

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7. A method of treating or inhibiting breast, uterine, ovarian, endometrial, or prostate cancer which comprises administering a compound formula 1 having the structure



wherein

R_1 , and R_2 are each, independently, hydrogen, alkyl, substituted alkyl, hydroxy, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, heteroarylalkyl, and alkynyl; or

R_1 and R_2 are taken together form a ring and together contain $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CMe}_2\text{CH}_2\text{CH}_2-$, $-\text{O}(\text{CH}_2)_p\text{CH}_2-$, $\text{O}(\text{CH}_2)_q\text{O}-$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{NR}_7\text{CH}_2\text{CH}_2-$; or

R_1 and R_2 are a double bond, said double bond having two methyl groups bonded to the terminal end, having a cycloalkyl group bonded to the terminal end, having an oxygen bonded to the terminal end, or having a cycloether bonded to the terminal end;

R_7 is hydrogen or alkyl of 1-6 carbon atoms;

$n = 1-5$;

$p = 1-4$;

$q = 1-4$;

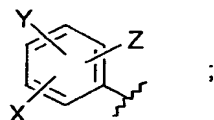
R^3 is hydrogen, hydroxyl, NH_2 , alkyl, substituted alkyl, alkenyl, alkynyl, substituted or, COR^A ;

R^A is hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

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R^4 is hydrogen, halogen, -CN, -NH₂, alkyl, substituted alkyl, alkoxy, aminoalkyl, or substituted aminoalkyl;

R^5 is a trisubstituted phenyl ring having the structure,



X is halogen, OH, -CN, alkyl, substituted alkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, S(O)alkyl, S(O)₂alkyl, aminoalkyl, substituted aminoalkyl, -NO₂, perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, thioalkoxy, -COR^B, -OCOR^B, or -NR^CCOR^B;

R^B is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

R^C is hydrogen, alkyl, or substituted alkyl;

Y and Z are each, independently, hydrogen, halogen, -CN, -NO₂, alkoxy, alkyl, or thioalkyl; or

R^5 is a five or six membered heteroaryl ring containing 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO₂ and NR⁶ with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, NO₂, alkyl, alkoxy, aminoalkyl, COR^D, and NR^ECOR^D;

R^D is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

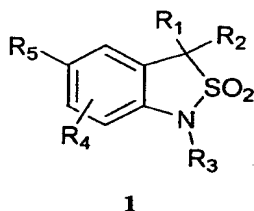
R^E is hydrogen, alkyl, or substituted alkyl;

R^6 is hydrogen, alkyl, alkoxycarbonyl, or is absent when the nitrogen of NR⁶ is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof, to said mammal.

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8. A method of providing contraception in a mammal in need thereof, which comprises administering an effective amount compound formula 1 having the structure



wherein

R_1 , and R_2 are each, independently, hydrogen, alkyl, substituted alkyl, hydroxy, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, arylalkyl, heteroarylalkyl, and alkynyl; or

R_1 and R_2 are taken together form a ring and together contain $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CMe}_2\text{CH}_2\text{CH}_2-$, $-\text{O}(\text{CH}_2)_p\text{CH}_2-$, $\text{O}(\text{CH}_2)_q\text{O}-$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{NR}_7\text{CH}_2\text{CH}_2-$; or

R_1 and R_2 are a double bond, said double bond having two methyl groups bonded to the terminal end, having a cycloalkyl group bonded to the terminal end, having an oxygen bonded to the terminal end, or having a cycloether bonded to the terminal end;

R_7 is hydrogen or alkyl of 1-6 carbon atoms;

$n = 1-5$;

$p = 1-4$;

$q = 1-4$;

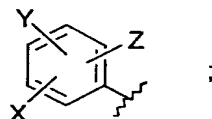
R^3 is hydrogen, hydroxyl, NH_2 , alkyl, substituted alkyl, alkenyl, alkynyl, substituted or, COR^A ;

R^A is hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

- 30 -

R^4 is hydrogen, halogen, -CN, -NH₂, alkyl, substituted alkyl, alkoxy, aminoalkyl, or substituted aminoalkyl;

R^5 is a trisubstituted phenyl ring having the structure,



X is halogen, OH, -CN, alkyl, substituted alkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, S(O)alkyl, S(O)₂alkyl, aminoalkyl, substituted aminoalkyl, -NO₂, perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, thioalkoxy, -COR^B, -OCOR^B, or -NR^CCOR^B;

R^B is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

R^C is hydrogen, alkyl, or substituted alkyl;

Y and Z are each, independently, hydrogen, halogen, -CN, -NO₂, alkoxy, alkyl, or thioalkyl; or

R⁵ is a five or six membered heteroaryl ring containing 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO₂ and NR⁶ with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, NO₂, alkyl, alkoxy, aminoalkyl, COR^D, and NR^ECOR^D;

R^D is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

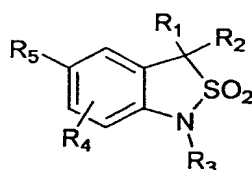
R^E is hydrogen, alkyl, or substituted alkyl;

R⁶ is hydrogen, alkyl, alkoxycarbonyl, or is absent when the nitrogen of NR⁶ is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof, to said mammal.

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9. A pharmaceutical composition, which comprises a compound formula 1 having the structure



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wherein

R_1 , and R_2 are each, independently, hydrogen, alkyl, substituted alkyl, hydroxy, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroarylalkyl, and alkynyl; or

R_1 and R_2 are taken together form a ring and together contain $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CMe}_2\text{CH}_2\text{CH}_2-$, $-\text{O}(\text{CH}_2)_p\text{CH}_2-$, $\text{O}(\text{CH}_2)_q\text{O}-$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{NR}_7\text{CH}_2\text{CH}_2-$; or

R_1 and R_2 are a double bond, said double bond having two methyl groups bonded to the terminal end, having a cycloalkyl group bonded to the terminal end, having an oxygen bonded to the terminal end, or having a cycloether bonded to the terminal end;

R_7 is hydrogen or alkyl of 1-6 carbon atoms;

$n = 1-5$;

$p = 1-4$;

$q = 1-4$;

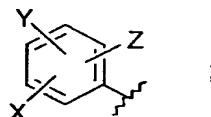
R^3 is hydrogen, hydroxyl, NH_2 , alkyl, substituted alkyl, alkenyl, alkynyl, substituted or, COR^A ;

R^A is hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

- 32 -

R^4 is hydrogen, halogen, -CN, -NH₂, alkyl, substituted alkyl, alkoxy, alkoxy, aminoalkyl, or substituted aminoalkyl;

R^5 is a trisubstituted phenyl ring having the structure,



X is halogen, OH, -CN, alkyl, substituted alkyl, alkoxy, substituted alkoxy, thioalkyl, substituted thioalkyl, S(O)alkyl, S(O)₂alkyl, aminoalkyl, substituted aminoalkyl, -NO₂, perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, thioalkoxy, -COR^B, -OCOR^B, or -NR^CCOR^B;

R^B is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

R^C is hydrogen, alkyl, or substituted alkyl;

Y and Z are each, independently, hydrogen, halogen, -CN, -NO₂, alkoxy, alkyl, or thioalkyl; or

R^5 is a five or six membered heteroaryl ring containing 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO₂ and NR⁶ with said ring carbons being optionally substituted with one or two substituents independently selected from the group consisting of hydrogen, halogen, CN, NO₂, alkyl, alkoxy, aminoalkyl, COR^D, and NR^ECOR^D;

R^D is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, alkoxy, substituted alkoxy, aminoalkyl, or substituted aminoalkyl;

R^E is hydrogen, alkyl, or substituted alkyl;

R^6 is hydrogen, alkyl, alkoxycarbonyl, or is absent when the nitrogen of NR⁶ is bonded to a ring double bond;

or pharmaceutically acceptable salt thereof and a pharmaceutical carrier.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 00/11823

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D275/06 C07D413/04 A61K31/428 A61P15/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 11264 A (SMITHKLINE BEECHAM CORP ; WIDDOWSON KATHERINE L (US); NIE HONG (US)) 11 March 1999 (1999-03-11) claims	1,9
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

5 September 2000

Date of mailing of the international search report

21/09/2000

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INTERNATIONAL SEARCH REPORT

Int. Patent Application No.
PCT/US 00/11823

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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